64. The composition of claim 61 wherein said nucleic acid has at least one chemical modification selected from the group consisting of a modified nucleobase, a modified sugar residue, and a modified backbone linkage.

65. The composition of claim 64 wherein said nucleic acid has at least one chemical modification selected from the group consisting of a cytosine to 5-methyl-cytosine substitution, a phosphorothioate linkage and a 2'-methoxyethoxy modification.--

REMARKS

Claims 1-40 were pending in the present application. Claims 2, 4, 6-11, 14-22, 28-31, 34 and 39 have been cancelled without prejudice to their presentation in another application. Claims 1, 3, 5, 23-27 and 38 have been amended herein. New claims 41-65 have been added. Upon entry of the present Amendment, claims 1, 3, 5, 12, 13, 23-27 32, 33, 35-38 and 40-65 will be pending.

As a preliminary matter, Applicants thank the Examiner for allowing time to interview the present application on August 3, 2000. It was agreed that Applicants would be able to file a declaration showing evidence of enablement following Applicants' receipt of a forthcoming Office Action. Applicants' undersigned representative called the Examiner November 3, 2000 to point out that the Examiner, despite agreeing to provide Applicants an opportunity to file such a declaration, mailed a Final Rejection. Applicants thank the Examiner for indicating that the enclosed declaration would be considered. As recommended in the Advisory Action, the Declaration has been signed by both inventors.

In addition, the Advisory Action states that the amendment to claim 38 raises the issue of new matter. Claim 38 has been amended to recite that the pharmaceutical composition of claim 1, when administered to a mammal, results in "at least" about 15% bioavailability, support for which can be found at, for example, Example 4 of the specification where Formulation 3 resulted in 15% bioavailability. Thus, Applicants claim pharmaceutical compositions having 15%, or greater, bioavailability. As the Examiner is well aware, it is established law that limitations appearing in

claims need not be literally recited in the specification. The issue is not whether words used in the claims are present in the specification but, rather whether the concept expressed by the words is present. *In re Anderson*, 176 U.S.P.Q. 331 (C.C.P.A. 1973).

Applicants also enclose herewith a Supplemental Information Disclosure Statement.

I. Double Patenting Rejections

Claims 1-24 stand provisionally rejected under 35 U.S.C. §101 as claiming the same invention as that of claims 1-24 of co-pending application Serial No. 08/886,829. Applicants respectfully request that this rejection be deferred until allowable subject matter is indicated.

Claims 25-40 stand provisionally rejected under the doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1-47 of co-pending application Serial No. 08/886,829. Applicants respectfully request that this rejection also be deferred until allowable subject matter is indicated.

II. The Claims Are Clear And Definite

Claims 24 and 25 stand rejected under 35 U.S.C. §112, second paragraph, as allegedly being vague and indefinite. Applicants traverse the rejection and respectfully request reconsideration in view of the amended claims.

The Office Action asserts that recitation of "biological activity against" miscellaneous disorders and diseases resulting from infection by HIV or non-retroviral viruses is vague and definite because one skilled in the art would not know how to identify the "biological activity against" an unspecified disease caused by an unspecified organism. Although Applicants disagree with the Examiner's statements, solely to advance prosecution of the present application, Applicants have amended claim 24 to delete the objected language. Persons of ordinary skill would have no difficulty in determining whether a particular composition modulates the expression of a cellular adhesion protein or the rate of cellular proliferation.

The Office Action also asserts that recitation of "a disease or disorder that is treatable in whole or in part with one or more nucleic acids" is vague and definite because one skilled in the art would not know how to identify such a disease. Although Applicants, again, disagree with the Examiner's statements, solely to advance prosecution of the present application, Applicants have amended claim 25 to delete the objected language. Applicants have also amended claim 25 to recite a method of "enhancing penetration of a nucleic acid across the alimentary canal of an animal" by administering the pharmaceutical composition of claim 1, support for which can be found throughout the specification. Thus, claim 25 no longer contains any language objected to by the Examiner.

Accordingly, claims 24 and 25 are definite within the meaning of § 112. *In re Mercier*, 185 U.S.P.Q. 774 (C.C.P.A. 1975) (claims sufficiently define an invention so long as one skilled in the art can determine what subject matter is or is not within the scope of the claims). Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. §112, second paragraph, be withdrawn.

III. The Claimed Inventions Are Enabled

Claims 1-40 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to enable the claimed invention. Applicants traverse the rejection, as it may be applied to pending claims 1, 3, 5, 12, 13, 23-27 32, 33, 35-38 and 40-60, and respectfully request reconsideration because one skilled in the art would be able to practice the claimed inventions without being required to perform undue experimentation.

The Office Action asserts that while the specification "does provide teaching on the introduction of nucleic acids into the blood and generally into the organs of an animal via the enteric pathway," the Office Action continues to mistakenly assert that the specification does not teach how to treat since such practice is allegedly unpredictable. The Office Action further recites several factors which purportedly support the position taken in the Office Action. The Examiner is, again, reminded that Applicants need only enable one use for such pharmaceutical compositions and that **any utility** that Applicants enable for the claimed pharmaceutical compositions is sufficient for

purposes of enablement. In this respect, the Examiner's attention is drawn to amended claim 25 which recites a method of "enhancing penetration of a nucleic acid across the alimentary canal of an animal" by administering a pharmaceutical composition of claim 1. Applicants enclose herewith a Declaration of Dr. Hardee/Dr. Teng showing that the claimed pharmaceutical compositions, in fact, enhance penetration of a nucleic acid across the alimentary canal of an animal. Paragraphs 3-5 of the Declaration describe experiments whereby penetration of an oligonucleotide across the alimentary canal of rats and dogs is enhanced by delivery of the oligonucleotide along with at least two fatty acids. Such examples are also set forth in Applicants specification in Examples 3, 4 and 13. Thus, Applicants have clearly enabled one skilled in the art to enhance penetration of a nucleic acid across the alimentary canal of an animal by administering a pharmaceutical composition of claim 1 to the animal without requiring performance of undue experimentation. Accordingly, claim 25 is clearly enabled.

In addition, to the extent that the Examiner still takes the position that Applicants must demonstrate treatment, Applicants' previous enclosure of copies of 1) Monia *et al.*, *Nature Med.*, **1996**, *2*, 668, 2) Oberbauer *et al.*, *Proc. Natl. Acad. Sci. USA*, **1996**, *93*, 4903, 3) Monia *et al.*, *Proc. Natl. Acad. Sci. USA.*, **1996**, *93*, 15481, 4) Cucco *et al.*, *Cancer Res.*, **1996**, *56*, 4332, 5) Offensperger *et al.*, Antisense Therapy of Hepatitis B Virus Infection, **1996**, Agrawal Ed., Humana Press Inc. Tolowa, NJ, pp. 143-158, 6) Sun *et al.*, *Br. J. Pharmacol.*, **1996**, *118*, 131, 7) Neurath *et al.*, *Nature Med.*, **1996**, *2*, 998-1004, 8) Leonetti *et al.*, *J. N.C.I.*, **1996**, *88*, 419, and 9) Del Bufalo *et al.*, *Br. J. Cancer*, **1996**, *74*, 387, contrary to the assertions in the Office Action, provides a nexus between the successful enhancement of oligonucleotide penetration across the alimentary canal in an animal and treatment of an animal. Indeed, each reference demonstrates successful administration of pharmaceutical nucleic acids via the bloodstream or local administration. Each of these references shows that oligonucleotides administered to the bloodstream, in fact, reach their target destinations as well as have their intended effects on the target. Since the Office Action admits that Applicants have enabled one skilled in the art to "introduce nucleic acids into the blood and generally into the organs of an animal via the enteral pathway," and since the state of the art at the time the application

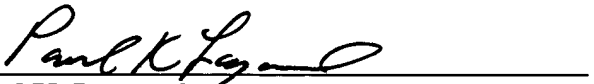
was filed demonstrates that oligonucleotides administered into the blood reach their intended target and have, for example, anti-tumor activity, an appropriate nexus to treatment has been established. Further, since nucleic acids have been shown to have at least some therapeutic value, pharmaceutical compositions comprising penetration enhancers and the nucleic acids are also enabled. Thus, one skilled in the art is not required to perform any amount of undue experimentation in order to practice the claimed invention.

In view of the foregoing, Applicants respectfully request that the rejection under 35 U.S.C. §112, first paragraph, be withdrawn.

IV. Conclusion

It is respectfully submitted that this application is now in condition for allowance. Accordingly, an indication of allowability and an early Notice of Allowance are respectfully requested.

Respectfully submitted,



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